

to further improve the biodistribution of the ligands of Harris by conjugating a targeting agent thereto as shown by Fritzberg. Finally, the Examiner opines that hindsight reconstruction is proper under certain circumstances, citing *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). This rejection is respectfully traversed.

1. **The Examiner cannot ignore the express limitation to diamine chelators in Harris.**

At page 2 of the Office Action, the Examiner asserts that:

[a]lthough the preferred embodiments of the Harris invention may be diamine or diaminedithiol, there are no provisos set forth in the description of the formula which limits the formula to such compounds.

This assertion is simply not supported by the plain words of the reference, which repeatedly describes the compounds as "diaminethiol"<sup>1</sup>, "diaminedithiol"<sup>2</sup>, or "diamidodithiol"<sup>3</sup>. No reasonable chemist would ignore the express limitations of the Harris formula, particularly in view of the Harris disclosure that distinguishes diaminedithiol and diamidodithiol. A monoamine, diamide, thiol chelating compound is not even an unpreferred embodiment of Harris because of the specific limitations expressly set forth in the disclosure. The Examiner's position has no basis in logic or sound scientific reasoning, and it cannot support a *prima facie* rejection under § 103. *In re Soli*, 137 U.S.P.Q. 797, 801 (CCPA 1963).

The Examiner is correct that a reference may be relied upon for all that it would reasonably have suggested to those of ordinary skill. However, the citation of *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 U.S.P.Q.2d 1843 (Fed.Cir. 1989), fails to consider the entirety of the caselaw set forth therein. In particular, *Merck & Co. Inc. v. Biocraft Laboratories Inc.* states that "**all disclosures of the prior art, including unpreferred embodiments, must be considered**", *Id.* at 1846 (*emphasis added*). Thus the Examiner must consider the express Harris limitations to ester-substituted diaminethiols or

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<sup>1</sup> See, col. 3, line 17 and line 66; col. 4, line 48; col. 6, line 5; col. 9, line 42 and line 50; col. 10, line 6, line 15, line 62, and line 67.

<sup>2</sup> See, col. 4, line 60, line 61, line 65; col. 5, line 3, line 7, line 47, line 52, line 57; col. 6, line 14, line 16, line 21, and line 63; col. 7, line 37, line 53, line 55; col. 11, line 6, line 35, line 44, line 50; col. 8, line 7 and line 44.

<sup>3</sup> See, col. 8, line 31, line 46 and line 66.

diamidodithiols, which precludes an interpretation of the formula that encompasses the monoamine, diamide, single thiol metal chelator of the present invention.

**2. Neither reference provides motivation for the proposed combination.**

At pages 3-4 of the Office Action, the Examiner states that

[a]lthough the ligands may distribute in the kidneys, one of ordinary skill in the art would have been motivated to conjugate a targeting ligand to such chelators to gain the advantages of, 1) further increasing the organ (kidney) specificity or 2) target other organs or tissues with said ligands, as taught by, *inter alia*, Fritzberg.

Harris is completely devoid of any teaching or suggestion of a target tissue other than kidney. It is notable that U.S.Pat.No. 5,091,514 (Fritzberg '514) issued on February 25, 1992, well before the filing date of Harris (December 31, 1992). Harris thus had constructive knowledge of Fritzberg '514. At col. 2, lines 37-40, Harris cites European patent application 73424 [*sic*-173424] as disclosing the complex  $^{99m}\text{Tc}$ -MAG3. A copy of EP 173424 is submitted herewith as Exhibit A, for the convenience of the Examiner. Exhibit A also includes a copy of U.S.Pat.No. 4,980,147 (Fritzberg '147), which claims priority to USSNs 733,481 and 624,098, as does EP 173,424. These patents are submitted as evidence that Fritzberg's work in the area of  $^{99m}\text{Tc}$  chelators was known to Harris. A reasonable inference can be made from Harris' constructive knowledge of Fritzberg '514 and his failure to disclose it that Harris chose **not** to direct those of skill to chelators linked to an additional targeting agent.

While Fritzberg '514 generally discloses the desirability of localizing radionuclides at target organs, the only specific targets identified in the secondary reference are "lymph node pathology, deep venous thrombi and the detection and staging of neoplasms"<sup>4</sup>, "tumors"<sup>5</sup>, "cancer site"<sup>6</sup>, "cancer cell-associated antigens"<sup>7</sup>, and "tumor-associated antigen"<sup>8</sup>. Fritzberg '514 identifies copending application USSN 624,098, one of the priority applications of EP 173,424 and Fritzberg '147, as relevant literature disclosing technetium

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<sup>4</sup> See, col. 1, line 65-col. 2, line 2.

<sup>5</sup> See, col. 2, line 4.

<sup>6</sup> See, col. 7, lines 10-11.

<sup>7</sup> See, col. 7, line 14.

derivatives of MAG3 for evaluating renal function<sup>9</sup>. However, even though Fritzberg '514 considered the renal function chelator to be relevant, kidney was not specified as a target organ. A reasonable inference can thus be made that Fritzberg '514 does not direct those of skill to use the thiotriaza chelator/polypeptide conjugates to enhance biodistribution of radionuclides into the kidney.

As the Board of Patent Appeals and Interferences has stated:

[I]n order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. (*citations omitted, emphasis in original*).

*Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1301 (B.P.A.I. 1993). More recently, the Federal Circuit has expanded on this concept.

The mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination. (*citation omitted, emphasis in original*).

*In re Deuel*, 34 U.S.P.Q.2d 1210, 1214 (Fed.Cir. 1995).

In the instant rejection, the Examiner has done no more than conjecture that one of ordinary skill would have been led to the combine the references, since neither of the cited references contains any teaching, suggestion, incentive or inference to support the combination. The Examiner's conjecture does not constitute evidence that one of ordinary skill would have been led to the presently claimed invention. Neither of the references contains a suggestion of the desirability of the proposed combination, and in fact the absence of such a suggestion can reasonably be inferred to direct those of skill away from the combination.

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<sup>8</sup> See, col. 7, line 22.

<sup>9</sup> See, col. 1, lines 53-56.

**3. The generic disclosure of Harris, when applied to Fritzberg, does not direct those of skill to the presently claimed invention.**

The Examiner has cited *In re Susi*, 169 USPQ 423 (CCPA 1971) and *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed.Cir. 1994) to support the position that examples and preferred embodiments do not constitute a teaching away from a broader disclosure of nonpreferred embodiments. As discussed above, in light of Harris' explicit limitation of the formula to "diaminethiol", "diaminedithiol, and "diamidodithiol" embodiments, the monoamine, diamide thiol chelator of the present claims cannot logically be considered to be even an nonpreferred embodiment of the Harris invention. Further, the cited cases do not support the Examiner's position.

The facts of *In re Susi* can be distinguished from the instant fact pattern. The claims of *In re Susi* were directed to a polymer stabilized by a combination of a substituted phenol with certain benzylidene malonate acid di-esters. 169 U.S.P.Q. at 425. The polymers stabilized fell within the genus of plastics. *Id.* Two primary references were cited, the first of which (Knapp) disclosed stabilization of plastics from ultraviolet light induced degradation by a combination of a nitrophenol or a formylphenol with benzylidene malonate acid di-esters which contained an additional hydroxyl substitution on the benzene ring. *Id.* The second primary reference (Lauerer) disclosed plastic compositions containing ultraviolet light absorbers having a generic formula which encompassed benzylidene malonate acid di-esters. *Id.* The secondary reference (Costello) disclosed protection of polystyrene from ultraviolet light-induced deterioration by addition of a trialkyl phenol, in particular 2,4,6-tri-*t*-butyl phenol, which was recited in two of the applicant's dependent claims. *Id.* at 426.

Thus in *In re Susi* the cited prior art supported the examiner's combination, since each reference was directed to precisely the same problem (stabilization of plastics from UV degradation); the primary references disclosed the benzylidene malonate acid di-esters; Knapp disclosed use of the benzylidene malonate acid di-ester in combination with a substituted phenol; and the secondary reference disclosed use of the same trialkylphenol as the applicant recited in his dependent claims. Further, as pointed out in

*In re Grabiak*, 226 U.S.P.Q. 870, 873 (Fed.Cir. 1985), the *In re Susi* applicant conceded that the presence of the hydroxyl group in the Knapp compound was "of little importance".

In contrast, Harris and Fritzberg '514 are not directed to the same imaging indications; Harris and Fritzberg '514 disclose formulae which differ from the presently claimed formula; and Applicants have made no concessions regarding the differences between the claimed compounds and those of the prior art.

The facts of *In re Gurley* also differ from those of the instant fact pattern. The claims of *In re Gurley* were directed to an epoxy based printed circuit material for forming circuit boards. The cited reference, Yamagouchi, disclosed printed circuit material comprising a fibrous substrate impregnated with a polyester-imide resin. 31 U.S.P.Q.2d at 1131. Yamagouchi also disclosed that use of epoxy-impregnated fibrous substrate for making circuit boards was known, but that such circuit boards were inferior to those impregnated with polyester-imides. *Id.* Gurley's argument that Yamagouchi's statement constituted a teaching away from use of epoxy was unsuccessful, because Gurley did not distinguish his epoxy product from the product described in the reference, and he "asserted no discovery beyond what was known to the art". *Id.* at 1132.

*In re Gurley* is instructive in that the case defines a "teaching away".

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

*Id.* at 1131. The Examiner's attention is directed to *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 col. 2 (Fed.Cir. 1994) which states

[g]iven the vast number diphenols encompassed by the generic diphenol formula in Knapp, and the fact that the diphenols that Knapp specifically discloses to be "typical" "preferred" and "optimum" are different from and more complex than bisphenol A [the compounds at issue], we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A. A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly

when that disclosure indicates a preference leading away from the claimed compounds.

The Harris disclosure appearing at col. 3, line 16 to col. 4, line 45 is no more than a laundry list of possible substitutions in a large genus of ester substituted diaminethiols for complexing <sup>99m</sup>Tc. Harris is devoid of any teaching or suggestion of a specific path that should be selected to obtain the Fritzberg '514 formula from the many possibilities set forth in the laundry list. Harris is also devoid of any teaching or suggestion of a specific path which would direct those of skill to combine Harris with Fritzberg '514 to obtain the presently claimed invention.

**4. The present facts do not justify hindsight reconstruction of the claimed invention from the cited references.**

Citing *In re McLaughlin*, 443 F.2d 1392, 170 U.S.P.Q. 209 (CCPA 1971) the

Examiner has opined that

...so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

Current Federal Circuit precedent does not support the Examiner's contention that hindsight reconstruction of an invention is appropriate under any circumstances. Moreover, in maintaining the instant rejection, the Examiner has clearly gleaned the presently claimed formula from the Applicants' disclosure, since the formula is not taught or suggested in Harris or Fritzberg. The Examiner has constructed the rejection as follows:

- by ignoring the express limitation to diaminethiol, diaminedithiol, or diamidodithiol chelators;
- by substituting the Harris formula to obtain the presently claimed formula; and
- by combining Fritzberg with the improperly substituted Harris formula.

The Federal Circuit has recently reiterated its caution against the hindsight trap in *In re Dembiczak*, \_\_\_\_ U.S.P.Q.2d \_\_\_\_, Adv. Sheet 98-1498 at pages 7-8 (Fed.Cir. April 28, 1999).

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed.Cir. 1998) (describing "teaching or suggestion or motivation [to combine] as an "essential evidentiary component of an obviousness holding"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 U.S.P.Q.2d 1453, 1459 (Fed.Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed.Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed.Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 U.S.P.Q. 657, 667 (Fed.Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of the combination"); See also *Graham*, 383 U.S. at 18, 148 U.S.P.Q. at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight.

The Court has further elaborated on hindsight analysis:

. . . an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." (*citation omitted*)

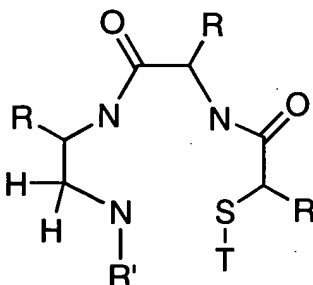
*In re Rouffet*, 47 U.S.P.Q.2d at \_\_\_\_, Adv. Sheet 97-1492 at page 11.

Even if the language of *In re McLaughlin* referenced by the Examiner continues to be applicable law, the Examiner's attention is directed to the fact that the

invention in *McLaughlin* was characterized by the Court as involving "only relatively simple mechanical concepts", 443 F.2d at 1395<sup>10</sup>, in contrast to the present chemical invention. The Examiner's attention is directed to the Court's precaution stated in *In re Grabiak*, 226 U.S.P.Q. at 872: "... generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *See also, In re Jones*, 21 U.S.P.Q.2d 1941, 1943 (Fed.Cir. 1992). Regardless of the extent to which hindsight reconstruction in a simple mechanical case is appropriate, the law does not support use of a chemical application as a blueprint to reconstruct a chemical invention from isolated disclosures in the prior art.

**5. The combination of Harris and Fritzberg does not yield the present invention.**

As Applicants have previously pointed out, even if the Harris general formula is substituted in such a way that it yields the Fritzberg formula, thus forming the basis of a proper combination, the result is not the presently claimed invention. If one X of the Fritzberg formula is substituted as H<sub>2</sub> to form a monoamine, diamide, thiol chelator, Fritzberg's formula has the configuration set forth below.

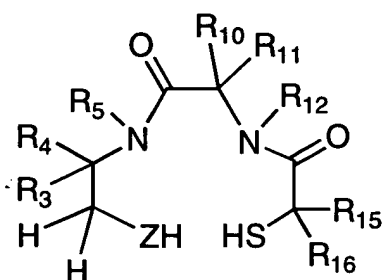


The formula of Harris is substituted as follows to yield the Fritzberg formula:

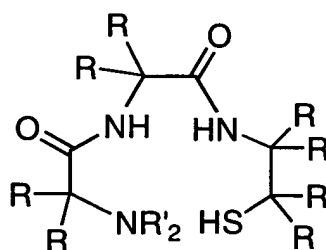
<sup>10</sup> Applicants question the continued viability of *McLaughlin* in light of the fact that the subject matter of the *In re Dembiczak* application was a Halloween-style pumpkin trash bag. Adv. Sheet at page 1.



$R_1$  and  $R_2$  must be H;  $n$  must be 0;  $R_6$  and  $R_7$  must form an oxygen atom;  $R_{13}$  and  $R_{14}$  must form an oxygen atom; and  $S$  must be exchanged with  $Z$ . The structure resulting from these substitutions is shown below.



In contrast, the chelator of claim 2 (shown with the  $n$ ,  $m$ , and  $p$  variables each equal to 0 so that comparison with Fritzberg is facilitated) is set forth below.



It is readily apparent that the structures of the cited references, when properly combined, do not teach or suggest the chelator of the present claims. See, *In re Mayne*, 41 U.S.P.Q.2d 1451, 1455 (Fed.Cir. 1997); *In re Jones*, 21 U.S.P.Q.2d 1941, 1944 (Fed.Cir.1992).

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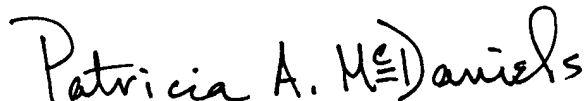
**Terminal Disclaimer**

In order to facilitate prosecution, a Terminal Disclaimer over USSN 08/092,355 and U.S.Pat.No. 5,620,675 is included with this Amendment.

In light of the arguments set forth above, Applicants submit that the rejection contained in the final Office Action of April 9, 1999 should be withdrawn and that the present claims are in condition for allowance or appeal. If the Examiner wishes to discuss this application further, he is requested to contact the undersigned attorney. If any additional fee is due with regard to this submission, authorization is hereby given to charge such fee, or to credit any overpayment, to Deposit Account No. 50-0452.

Respectfully submitted,

DIATIDE, INC.

A handwritten signature in black ink that reads "Patricia A. McDaniels". The signature is written in a cursive style with a large, looped "P" and a stylized "McDaniels".

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